REMARKS

Claims 1 and 10 have been amended to further clarify the invention. Claim 6 has been canceled. New claims 15-18 have been added. Support for the amendments to claims 1 and 10 can be found in canceled claim 6. Support for new claims 15-18 can be found in the specification, at page 4, lines 2-8. The claim amendments and cancellations are made without prejudice to the filing of continuing applications. No new matter is added by the amendments. With the amendments, claims 1-5, 7-11, and 15-18 are pending.

Claims 1-9 stand rejected under 35 U.S.C. § 112, first paragraph, as not being enabled for prophylaxis of an endothelin-mediated disorder; and claims 1-11 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over EP 0 882 719 (Harada '719) and WO 98/57938 (Harada '938). Each of these rejections is addressed below.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-9 stand rejected under § 112, first paragraph, with the Office contending that while the claims are enabled for the treatment of an endothelin-mediated disorders, the claims are not enabled for the prophylaxis of such disorders.

In order to expedite prosecution of this application, and without conceding the rejection, Applicants have amended claim 1 to remove the term "prophylaxis." Withdrawal of the rejection is therefore in order and is respectfully requested.

Rejection Under 35 U.S.C. § 103

Claims 1-11 continue to stand rejected under § 103 as being unpatentable over Harada '719 and Harada '938. In response to Applicants previous arguments, the Office continues to take the position that the tested species are not reasonable representative of the genus claimed. In particular, the Office argues that the phenyl and naphthyl of the Ar group may be substituted with a great number of different and distinct species.

Applicants respectfully submit that the species of compounds tested for activity are representative of the genus of the claims, as amended. Under the present amendment, the Ar group has been limited to optionally substituted phenyl and optionally substituted naphthyl. In addition, the substituents on Ar have been limited to six preferred types of substituents. The claims, as amended, are therefore representative of the tested compounds.

The Office continues to allege that the limitation in claims 10-11 concerning free blood plasma concentration does not impart any physical or otherwise material limitation to the claimed composition that is not found in the prior art compositions. The Office also asserts that the results do not establish unexpected results for the composition, but only to the manner in which the composition is used. Applicants respectfully disagree.

Applicants respectfully point the Examiner's attention to the Patent Office's "Genus-Species Guidelines" for examining applications which contain claims to a species or a subgenus of chemical compositions, in view of a single prior art reference not expressly disclosing the particular claimed species or subgenus. See MPEP 2144.08. Under these guidelines, the Office may consider evidence that the claimed invention yields unexpectedly improved properties as indicative that the invention is not obvious over the reference. See *Id.*, and *In re Dillon*, 919 F.2d 688, 692-93 (Fed. Cir. 1990). Such evidence may be sufficient in itself to show non-obviousness. There is no requirement that the claims contain a material limitation not found in the prior art. Rather, it is the fact that the claimed species or subgeneric group itself yields unexpected results that provides the basis for non-obvious.

In the present case, Applicants have shown, and the Office concedes, that the manner in which the compositions are used establishes unexpected results. See Office Action of 7/29/04, page 4, 4th full paragraph. This showing of unexpected results is sufficient to overcome the obviousness rejection, as discussed above. The claim term regarding free blood plasma concentration is not required in the genus-species context, in view of the showing of unexpected results. Thus the Office's contention that this requirement does not impart a material limitation is not relevant in the present context.

Applicants further respectfully disagree with the distinction drawn by the Office between unexpected results of a composition and unexpected results for the manner in which the composition is used. See Id. A composition exhibits unexpected results through its properties. In the instant case, Applicants claimed subgeneric group provides compositions having longer duration of action resulting from free blood plasma concentration. See e.g., Applicants Office Action Response of July 21, 2003. This unexpected property of Applicants' claimed subgeneric group is not disclosed or suggested by the cited references. Further, as discussed above, the amended claims are commensurate in scope with the compounds exhibiting the unexpected results. Applicants claims, therefore, fall squarely within the genus-species context to which MPEP 2144.08 is addressed. Consequently, the claimed compositions are not obvious in view of the Harada references.

For at least the reasons discussed above, Applicants submit that the pending claims are not rendered obvious by the references. Withdrawal of the § 103 rejection of claims 1-11 is therefore respectfully requested.

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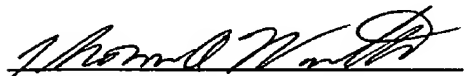
Applicants respectfully submit that all of the pending claims are in condition for allowance. Notice to this effect is respectfully solicited. Should the Examiner believe a discussion of this matter would be helpful, the Examiner is invited to telephone the undersigned at (269) 833-7914.

Respectfully submitted,



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